IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Himmelsbach, F. et al
Serial no.	:	10/693,069
Filed	:	October 24, 2003
For	:	Xanthine derivatives, the preparation thereof and their use as pharmaceutical compositions
Art Unit	:	1624
Examiner	:	Berch, Mark L.

DECLARATION UNDER RULE 132

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Frank Himmelsbach solemnly states and declares as follows:

1. My technical background is as follows: I am a trained chemist having received a doctorate (Dr. rer. nat.) in chemistry from the University of Konstanz, Germany in 1984 .

I did a postdoctoral study at the Imperial College London from September 1984 to December 1984. I joined the Department of Chemistry of Dr. Karl Thomae GmbH, Biberach/Riss, Germany in 1985 as Head of Laboratory, and I presently hold the position of Group Leader in the Department of Chemistry Research of Boehringer Ingelheim Pharma GmbH & Co. KG (formerly named Dr. Karl Thomae GmbH), Biberach/Riss, Germany.

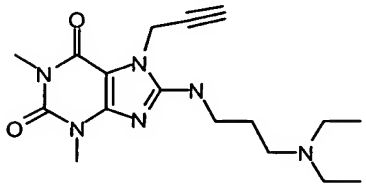
I am a member of the "Gesellschaft Deutscher Chemiker" (Society of German Chemists).

2. I am familiar with the subject matter of the above-noted patent application.

3. I am familiar with the Office Action dated 12/20/2002 in parent case 10/081,826 and the cited prior art document: JP 37-4895.

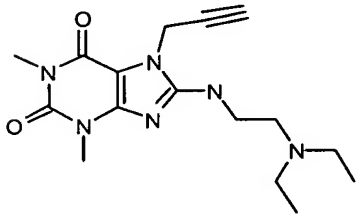
4. In my capacity as Group Leader in the Department of Chemistry Research of Boehringer Ingelheim I supervised the screening and evaluation of compounds under the research division's program directed to the development of compounds active against DPP-IV.

5. In the previous declaration I explained that our efforts to synthesize compound A:



which is described in JP 37-4895

and compound B:



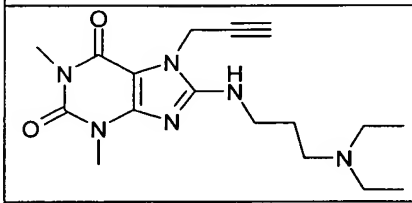
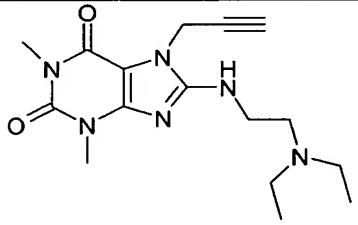
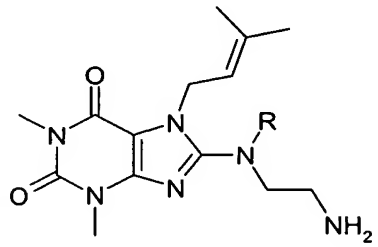
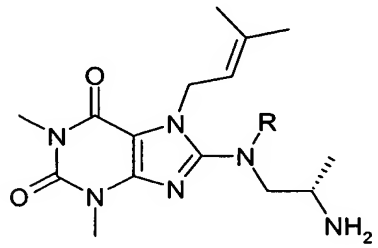
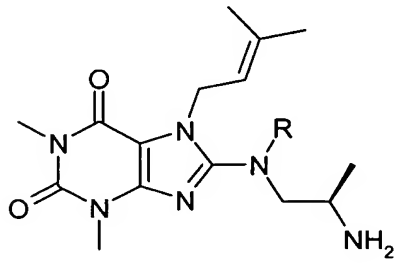
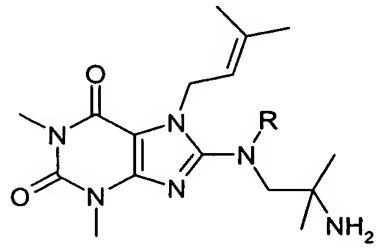
which is described in US 2,928,833 (Example XXIII)

according to the procedures as given in the above-mentioned documents failed.

In a further effort to obtain these compounds we varied the reaction conditions for the nucleophilic displacement of the halogen atom in position 8 of the xanthine scaffold by the respective amines. We found that the desired compounds are formed when the reaction is carried out in DMSO in the presence of sodium carbonate.

6. In order to demonstrate the unexpectedly improved activity against DPP-IV for the compounds of the present invention for all compounds where R^4 is an amino group substituted by R^{15} and R^{16} in the claims where R^{15} is other than hydrogen, the DPP-IV assay was performed.

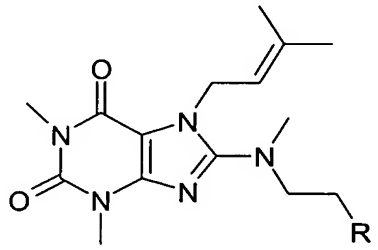
That, when the following compounds listed in the following table were screened in the DPP-IV Assay described in on pages 51 to 52 of the above-noted patent application, the results obtained are shown in the following table:

Structure	Example number	DPP-IV, IC_{50} [nM]
	Prior Art Compound from JP 37-4895	>10000
	Prior Art Compound from US 2,928,833	>10000
	R = hydrogen (not exemplified) R = methyl 1(35) R = ethyl 2(8)	4600 95 225
	R = hydrogen 1(136) R = methyl 1(79)	10440 275
	R = hydrogen 1(135) R = methyl 1(81)	1661 424
	R = hydrogen 1(134) R = methyl 2(112)	6977 381

7. The above-identified results are unexpected as there is no expectation that, for the claimed compounds, when R^4 is -N(CH_3)(R_{16}) and -N(CH_2CH_3)(R_{16}) substitution versus NH(R_{16}), this would improve the anti-DPP-IV activity.

8. The above-identified results are commensurate in scope for the claimed subject matter, as there is no reason to expect that other compounds wherein R^4 is an amino group substituted by R^{15} and R^{16} as given in the claims would not exhibit similar activity.

9. It is important to note that additional features of the Prior Art Compounds listed above may contribute to their low activity in the DPPIV-Assay. According to our knowledge a primary amino group for R^{17} is much preferred over a tertiary one:

Structure	Example number	DPP-IV, IC_{50} [nM]
	R = amino 1(35) R = dimethylamino 1(46)	95 >10000

10. The difference between the improved anti-DPP-IV activity of the compounds of the present invention over those of the prior art are significant. Accordingly, the consumer would prefer the more effective compound.

The undersigned petitioner declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Feb. 26, 2004 Signature: F. Himmelsbach

(Frank Himmelsbach)